

By cont  
contacting said duplex with an agent that digests the unhybridized RNA  
portion(s) of said duplex,  
denaturing said digested duplex,  
separating the denatured RNA fragments by size, and  
comparing the separated fragments to RNA fragments representative of  
normal RNA.

### REMARKS

The specification has been amended to include a sequence listing as required by 37 C.F.R. 1.821(c). Specifically, replacement pages 42-45 contain the sequence listing. Original pages 42-50 which contain the claims and abstract have been amended as pages 46-54. The contents of the sequences in the present application are identical to that of the diskette submitted in the parent application U.S.S.N. 07/989,160, filed Dec. 11, 1992 and issued as U.S. patent no. 5,429,923. Accordingly, reference is hereby made to that parent application in lieu of filing another diskette, under 37 C.F.R. § 1.821(e). The specification has also been amended to correct typographical errors.

Claims 1-30, and 32-46 are pending in the present application. Claims 33, 36 and 39 have been amended to more particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Support for these amendments can be found in the claims as originally filed.

Claims 44-46 have been added. New claim 44 is drawn to the non-invasive method for diagnosing hypertrophic cardiomyopathy described in claim 18 wherein the cell sample is obtained from nucleated blood cells. Support for new claim 44 can be found in the specification at, for example, page 4, lines 16-21. New claim 45 is drawn to the method for identifying a hypertrophic cardiomyopathy-associated mutation in a DNA sequence present in a genomic DNA sample which is described in claim 24 wherein the

genomic DNA sample is obtained from nucleated blood cells. Support for new claim 45 is found in the specification at, for example, page 4, lines 16-21. New claim 46 is drawn to the method for identifying a hypertrophic cardiomyopathy-associated mutation in a DNA sequence present in a genomic DNA sample which is described in claim 45 wherein said detecting comprises the steps of contacting said duplex with an agent that digests the unhybridized RNA portion(s) of said duplex, denaturing said digested duplex, separating the denatured RNA fragments by size, and comparing the separated fragments to RNA fragments representative of normal RNA. Support for new claim 46 is found in the specification at, for example, page 13, lines 22-30.

Cancellation of and/or amendment to any of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation of and/or amendment to the claims are being made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application. No new matter has been added.

Applicants acknowledge the Examiner's withdrawal of the rejection of claim 36 under 35 U.S.C. §101, the withdrawal of the rejection of claims 6, 13-23, 26, 37 and 38 under 35 U.S.C. §112 second paragraph, the withdrawal of the rejection of claims 1-31 and 36-38 under 35 U.S.C. §102(a) as anticipated by Rosenzweig and as anticipated by Watkins, the withdrawal of the rejection of claims 33-35 under 35 U.S.C. §103 over Rosenzweig or Watkins in view of the Stratagene Catalog, and the withdrawal of the rejection of claims 24-30 under 35 U.S.C. §102(b) in view of Almoguera *et al.*

Rejection of Claims 1-30 and 32-43 Under the Judicially Created Doctrine of Obviousness-Type Double Patenting

Claims 1-30 and 32-43 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,429,923. The Examiner maintains the rejection for reasons of record.

Accordingly Applicants again respectfully submit that a terminal disclaimer will be filed upon indication of allowable subject matter, if appropriate.

Rejection of Claim 36 Under 35 U.S.C. § 102(b)

Claim 36 is rejected under 35 U.S.C. § 102(b) as being anticipated by Eisenberg (March 1991) *Journal Molecular and Cellular Cardiology* 23:287-296. Specifically, the Examiner states that

Eisenberg teaches RNA probes complementary to the sequences of the  $\beta$ -MHC nucleic acids (see page 289). The probes are considered to have the property of being useful for facilitating diagnosis of hypertrophic cardiomyopathy because the probes of Eisenberg hybridize to and thereby are capable of detecting changes in the  $\beta$ -cardiac myosin heavy chain DNA.

It is the Examiner's further position that "it is a property of the probe disclosed by Eisenberg that it would be useful for diagnosing hypertrophic cardiomyopathy because the probe is capable of hybridizing to and detecting  $\beta$ -cardiac myosin heavy chain DNA." Applicants respectfully traverse this rejection.

Claim 36 is drawn to an isolated RNA probe having ribonucleotides arranged in a sequence which is complementary to at least a portion of  $\beta$ -cardiac myosin heavy-chain DNA. The probe is claimed as being useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being arranged in a sequence to detect a hypertrophic cardiomyopathy-associated mutation.

Eisenberg studied the distribution of myosin heavy chain mRNA in normal and hyperthyroid hearts. Eisenberg does not teach or suggest an RNA probe useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being arranged in a sequence to detect a hypertrophic cardiomyopathy-associated mutation as presently being claimed. Furthermore, Eisenberg teaches away from a probe being complementary to at least a portion of  $\beta$ -cardiac myosin heavy chain DNA in that the probe used in Eisenberg is not capable of distinguishing between  $\alpha$ - and  $\beta$ -myosin (see p. 284). Accordingly, Eisenberg fails to anticipate claim 36.

Rejection of Claims 37 and 38 Under 35 U.S.C. § 102(a)

Claims 37 and 38 are rejected under 35 U.S.C. § 102(a) as being anticipated by Friedman *et al.* (March-April 1992) *Basic Research Cardiology* 87:106-112. Specifically, the Examiner states that "Friedman teaches sets of nested PCR primers useful for the amplification of nucleic acids of  $\beta$ -MHC (see page 109)." It is the Examiner's further position that

... it is a property of the primers taught by Friedman that they are useful in the diagnosis of hypertrophic cardiomyopathy because the primers are capable of amplifying the  $\beta$ -MHC DNA and thereby could be used for diagnostic analysis of the sequences of the amplified  $\beta$ -MHC DNA.

Applicants respectfully traverse this rejection.

Claim 37 is drawn to at least two oligonucleotides which amplify  $\beta$ -cardiac myosin heavy-chain DNA. The set of oligonucleotide primers is claimed as being useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being **useful in the detection of a hypertrophic cardiomyopathy-associated mutation.**

Friedman *et al.* unsuccessfully sought to determine whether somatic mutation occurs in the gene for cardiac  $\beta$ -MHC, by studying biopsied myocardial tissue from patients afflicted with hypertrophic cardiomyopathy. Friedman *et al.* concluded that

"mutations in exon 13 of the cardiac  $\beta$  MHC could not be demonstrated in the myocardium of patients with HCM".

Accordingly, Friedman *et al.* do not teach or suggest a set of oligonucleotide primers useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being **useful in the detection of a hypertrophic cardiomyopathy-associated mutation.**

The mere use of nested primers does not anticipate the present invention, as Friedman *et al.* use this procedure merely to introduce a 50 bp GC clamp, to enable melting point analysis. Friedman *et al.* Do not teach or suggest the usefulness of these primers in the detection of hypertrophic cardiomyopathy-associated mutation.

Furthermore, the teachings of Friedman actually teach away from the claimed invention. Friedman studied seven patients with hypertrophic cardiomyopathy and concluded that "mutations in exon 13 of the cardiac B MHC could not be demonstrated in the myocardium of patients with HCM". Thus, Friedman does not teach or suggest the Applicants' invention which is drawn to a set of oligonucleotide primers useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being useful in the detection of a hypertrophic cardiomyopathy-associated mutation. Accordingly, Applicants request the Examiner to reconsider and withdraw the rejection of claims 37 and 38 under 35 U.S.C. §102(a).

Rejection of Claims 37 and 38 Under 35 U.S.C. § 102(b)

Claims 37 and 38 are rejected under 35 U.S.C. § 102(b) as being anticipated by Feldman (June 1991) *Circulation* 83:1866-1872. Specifically, the Examiner states that "Feldman teaches compositions comprising sets of PCR primers useful for the amplification of nucleic acids of  $\beta$ -MHC (see page 1867)." It is the Examiner's further position that

... it is a characteristic of the primers taught by Feldman that they are useful in the diagnosis of hypertrophic cardiomyopathy because the primers are capable of amplifying the  $\beta$ -MHC DNA and thereby could be used for diagnostic analysis of the sequences of the amplified  $\beta$ -MHC DNA."

Applicants respectfully traverse this rejection.

As set forth above, claim 37 is drawn to at least two oligonucleotides which amplify  $\beta$ -cardiac myosin heavy-chain DNA. The set of oligonucleotide primers is claimed as being useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being useful in the detection of a hypertrophic cardiomyopathy-associated mutation.

Feldman evaluated gene expression in failing human heart using the polymerase chain reaction. Feldman does not teach or suggest a set of oligonucleotide primers useful for facilitating the diagnosis of hypertrophic cardiomyopathy by being useful in the detection of a hypertrophic cardiomyopathy-associated mutation as presently being claimed. Amplification alone does not provide utility in the detection of mutations. Therefore, Feldman do not anticipate claims 37 and 38.

#### Rejections of Claims 33-35 under 35 U.S.C. § 103

Claims 33-35 are rejected under § 103 as being unpatentable over Geisterfer-Lowrance *et al.* in view of Almoguera and further in view of the Stratagene Catalog. Specifically, the Examiner states that Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy. The Examiner admits that Geisterfer-Lowrance does not teach detecting point mutations associated with hypertrophic cardiomyopathy by first amplifying sample  $\beta$ -MHC nucleic acids and performing a RNase protection assay.

The Examiner further states that Almoguera teaches methods for identifying gene mutations associated with genetically inherited diseases wherein the methods comprise

performing an RNase protection assay. Specifically, the Examiner states that the assay in Almoguera identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA.

From this the Examiner concludes that it would have been obvious

... to have modified the method of Geisterfer-Lowrance so as to have detected the mutations associated with hypertrophic cardiomyopathy in  $\beta$ -MHC nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay using a labeled RNA probe ... Modification of the method of Geisterfer-Lowrance ... would have resulted in a method for detecting point mutations in the  $\beta$ -MHC gene which required the use of the reagents of an RNA probe hybridizable to the  $\beta$ -MHC gene and a RNaseA for digesting unhybridized RNA. ...

The Examiner admits that the combined references do not teach packaging the reagents to practice the detection method or instructions for the detection method in a kit. However, the Examiner believes that reagent kits for performing nucleic acid diagnostic assays were conventional in the field of molecular biology at the time of the invention. In particular, the Examiner notes the Stratagene catalog.

From this, the Examiner concludes, it would have been prima facie obvious to have packaged the primers, RNA probe, and RNase in a kit. Also, the Examiner concludes that it would have been prima facie obvious to have included instructions in the kit.

It is the Examiner's still further position that

...in claims to products, such as kits, the intended use of the product carries no weight. While the teachings of Geisterfer-Lowrance may not have been sufficient to enable absolute diagnosis of HC, the prior art suggests use of the disclosed sequences to amplify  $\beta$ -MHC nucleic acids and to identify mutations. Accordingly, the prior art when considered as a whole would have suggested the claimed kits for the benefits of convenience and cost-effectiveness for practitioners of the art wishing to amplify and identify mutations in the  $\beta$ -MHC nucleic acid.

The proper inquiry under section 103 is whether the prior art would have suggested to one having ordinary skill in the art at the time of the invention the claimed method or kit for facilitating the diagnosis of hypertrophic cardiomyopathy and that there was a reasonable expectation of success for the claimed method or kit in view of the prior art. Applicants submit that the cited references fail to suggest the claimed invention. Furthermore, no reasonable expectation of success existed for formulating a method or kit for detecting the presence of mutations associated with hypertrophic cardiomyopathy in view of the cited references.

Geisterfer-Lowrance *et al.* disclose the detection of one point mutation associated with familial hypertrophic cardiomyopathy which occurs in the  $\beta$  cardiac myosin heavy chain gene of affected members of one family with FHC. The  $\beta$  cardiac myosin heavy chain gene mutation results in an Arg403Gln substitution in exon 13 of the  $\beta$  cardiac MHC protein. The mutation was detected in the course of providing a restriction map of the  $\alpha$  and  $\beta$  MHC genes by the fortuitous identification of a restriction site polymorphism in the  $\beta$  cardiac myosin heavy chain gene of an affected subject, and subsequent sequencing of a subcloned DNA fragment encompassing this mutation was then used to elucidate the amino acid substitution.

Geisterfer-Lowrance *et al.* demonstrate that affected members of a **single family** with FHC (Family A) have the mutation leading to the Arg403Gln substitution in the  $\beta$  cardiac myosin heavy chain protein. A concurrently published paper (Tanigawa *et al.*), which is referenced in Geisterfer-Lowrance *et al.*, demonstrates that afflicted members of a different family with FHC (Family B) have a mutation which produces an  $\alpha/\beta$  cardiac myosin heavy-chain hybrid gene.

At the time of the present invention, these were the only two families studied with regard to mutations associated with hypertrophic cardiomyopathy and these were the only two disease-associated mutations described in the art. Thus, at the time the invention was



made, it was possible that hypertrophic cardiomyopathy in other individuals (i.e., individuals who are not members of Family A or Family B) could be due to 1) a point mutation in amino acid residue 403 of the  $\beta$  cardiac myosin heavy chain protein; 2) an  $\alpha/\beta$  cardiac myosin heavy-chain hybrid gene; or 3) other mutations which had not been described in the art.

Furthermore, Geisterfer-Lowrance *et al.* acknowledge the absence of a reasonable expectation of success in formulating a method or kit for detecting the presence of mutations associated with hypertrophic cardiomyopathy. For example, Geisterfer-Lowrance *et al.* state at page 1004, lines 37-42, that

[s]ince the cardiac MHC gene mutations that cause FHC have been characterized in only two families, we cannot yet predict whether most affected individuals bear either of these two alleles (indicating that there is a strong founder effect) or whether the disease occurs principally as a result of new mutations.

Therefore, the teachings of Geisterfer-Lowrance *et al.* would not have suggested, to one of ordinary skill in the art at the time of the invention, the claimed methods for facilitating the diagnosis of hypertrophic cardiomyopathy, since it was unclear from Geisterfer-Lowrance *et al.* whether mutations in  $\beta$  cardiac myosin heavy chain DNA would be present in subjects having HC who were unrelated to Family A.

If, for example, all HC-associated mutations in individuals unrelated to Family A were in fact due to  $\alpha/\beta$  cardiac myosin heavy-chain gene fusions (as in Family B), then isolating  $\beta$  cardiac myosin heavy chain RNA from a blood sample from a subject and trying to detect the presence or absence of a hypertrophic cardiomyopathy-associated mutation in the RNA would likely be uninformative. Alternatively, if none of the HC-associated mutations in individuals unrelated to Family A were in fact due to mutations in  $\beta$ -cardiac MHC, as might have been found if these mutations occurred in genes encoding other sarcomeric proteins, then isolating  $\beta$  cardiac myosin heavy chain RNA from a blood

sample from a subject and trying to detect the presence or absence of a hypertrophic cardiomyopathy-associated mutation in the RNA would have been equally uninformative.

Prior to the present invention there were no extensive studies involving a large number of families which could establish that HC could commonly be caused by point mutations in the  $\beta$  cardiac myosin heavy chain gene. Geisterfer-Lowrance *et al.* do not teach or suggest that a correlation exists between the presence of a mutation in the  $\beta$  cardiac myosin heavy chain gene and the presence of hypertrophic cardiomyopathy in individuals unrelated to family A. Thus Geisterfer-Lowrance *et al.* do not teach or suggest that detection of a mutation in the  $\beta$  cardiac myosin heavy chain gene can be used to facilitate diagnosing the disease in a subject.

In contrast, the present invention discloses the study of twenty-five families with members having FHC. Further, twelve of the twenty-five families displayed point mutations in the  $\beta$  cardiac myosin heavy chain gene. Seven different point mutations, located in four different exons, were detected. (See Example 2, pages 34-38 of the specification). Furthermore, members of Family B (discussed above), who have an  $\alpha/\beta$  cardiac myosin heavy-chain hybrid gene, were found to also have a point mutation in their other  $\beta$  cardiac myosin heavy chain gene. Applicants have thus discovered that point mutations in the  $\beta$  cardiac myosin heavy chain gene are present in many individuals from unrelated families affected with hypertrophic cardiopathy (i.e., approximately 50 % of the patients examined), and in heretofore asymptomatic children from FHC-affected families in which the mutation in the  $\beta$  cardiac myosin heavy chain gene is present. Thus, the present invention shows that detection of these mutations can be used as an indicator of hypertrophic cardiopathy and for facilitating diagnosis of the disease.

It is only with Applicant's extensive analysis of families and individuals with HC that one would be motivated to detect mutations in the  $\beta$  cardiac myosin heavy chain gene in subjects unrelated to Family A as a basis for facilitating the diagnosis of the

disease in a subject. Moreover, it is only with this extensive analysis, and the provision of general methods, that one would have a reasonable expectation of success in facilitating diagnosis of HC in subjects unrelated to Family A by detecting mutations in the  $\beta$  cardiac myosin heavy chain gene.

The secondary references cited by the Examiner fail to cure the deficiencies of Geisterfer-Lowrance *et al.* Almoguera teaches the use of Rnase protection assays for identifying gene mutations. The Stratagene catalog discloses reagent kits for performing nucleic acid diagnostic assays. Neither of these references provides the motivation or expectation of success for formulating methods or kits for detecting mutations in the  $\beta$ -myosin cardiac heavy chain gene in subjects unrelated to the family studied in Geisterfer-Lowrance *et al.*

Furthermore, Applicants respectfully traverse the Examiner's argument that advantages of kits include merely issues of pre-assembly of specific reagents and reagent quality and compatibility assurance. The kits of the present invention facilitate diagnosis of HC that is caused by mutations in  $\beta$ -MHC, and thereby provide probes and primers suitable for diagnosis of FHC and for SHC. The Applicants traverse the Examiner's argument that the instructions included as part of the kits are not statutory patentable material, as kits for diagnosis of human disease require approval of a governmental regulatory agency, including approval of labels and other written materials. For example, the instructions that comprise a component of the present invention would guide the user in choice of one or more appropriate probes and primer components from among a product line consisting of alternative components, guided by the subject's family history of the disease. Further, conditions of pH, temperature, and ionic strength that can be optimized for use of a kit with particular primers and probes would enable successful application of the kits to a wider range of diagnostic use. Finally, as part of the printed

instruction for use if negative results were obtained, the instructions might include reference to additional materials for diagnosis of mutations in genes other than the  $\beta$ -MHC gene that can also underly HC. If positive results were obtained, the instructions might include reference to sources for subsequent genetic counseling and availability of maintenance regimens.

The components of the kits of the present invention, including the instructions, are thus entirely distinct from the components and instructions of the kits cited by the Examiner. Almoguera *et al.* and the Stratagene catalog alone or together neither teach nor suggest diagnosis of HC.

Rejection of Claims 36 and 39 Under 35 U.S.C. §112, Second Paragraph

Claims 36 and 39 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner states that the recitation of the term "by being arranged for use" is unclear as to what is intended to be meant by a probe being arranged for use in a detection method. The Examiner also states that the recitation of the term "said primers comprising at least two oligonucleotides" is not clear as to whether the claim is intended to be limited to primers which are made up of at least two of the recited oligonucleotides or if the claims are intended to be limited to sets of primers wherein the set comprises at least two of the recited oligonucleotides.

Applicants have amended the claims to delete the terms objected to by the Examiner. Therefore, the rejection is now moot.

Rejection of Claims 24-26, 28-30 and 43, and Rejection of Claim 27 Under 35 U.S.C.§103

Claims 24-26, 28-30, and 43 are rejected under 35 U.S.C. §103 as being unpatentable over Geisterfer-Lowrance *et al.* in view of Mullis. Specifically, the Examiner states that Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy which comprise detecting the presence of point mutations in  $\beta$ -MHC nucleic acids.

The Examiner admits that Geisterfer-Lowrance does not teach amplifying the sample  $\beta$ -MHC nucleic acid prior to determining the sequence of the DNA. However, the Examiner states that Mullis teaches methods for amplifying nucleic acids using PCR and applies these methods to assays to detect the presence of point mutations in the nucleic acids which are associated with genetic diseases.

From this, the Examiner concludes that it would have been obvious

... to have modified the method of Geisterfer-Lowrance so as to have amplified the  $\beta$ -MHC nucleic acids prior to sequence analysis in order to have increased the quantity of the target DNA and thereby to have increased the overall sensitivity of the detection of hypertrophic cardiomyopathy associated point mutations in the  $\beta$ -MHC nucleic acids.

As stated in Applicants' remarks above, the substance of which is reiterated here, Geisterfer-Lowrance *et al.* fail to suggest the claimed invention and provide no reasonable expectation of success for formulating a method or kit for detecting the presence of mutations associated with hypertrophic cardiomyopathy. Mullis *et al.* fail to cure the deficiencies of Geisterfer-Lowrance *et al.*

Mullis, *et al.* discuss the amplification method of PCR by demonstrating, for example, amplification of a 94 bp length sequence of the  $\beta$ -globin gene; amplification of a 240 bp product; use of a 40 bp probe, and amplification of a 110 bp nested inner product. Mullis *et al.* do not make up for the deficiencies of Geisterfer-Lowrance *et al.*

Applicants respectfully point out that mere amplification of  $\beta$ -MHC nucleic acids prior to sequence analysis in order to increase the quantity of target DNA, does not comprise the significant difference between Geisterfer-Lowrance *et al.* and the present invention. Mullis *et al.* neither teach nor suggest how to diagnose a subject who might carry a mutation within a 30,000 bp gene, nor whether to have confidence in the result. Neither reference teaches a method of diagnosing of a mutation in a gene affecting cardiac structure, by amplification of human genomic DNA from a sample taken non-invasively. For at least these reasons, Geisterfer-Lowrance *et al.* in combination with Mullis *et al.* fail to render the present invention obvious.

Rejection of Claim 27 Under 35 U.S.C. §103

Claim 27 is rejected under 35 U.S.C. §103 as being unpatentable over Geisterfer-Lowrance in view of Almoguera. Specifically, the Examiner states that Geisterfer-Lowrance teaches methods for detecting the presence of mutations associated with hypertrophic cardiomyopathy which include detecting the presence of point mutations in the  $\beta$ -MHC nucleic acids.

The Examiner admits that Geisterfer-Lowrance does not teach detecting point mutations associated with hypertrophic cardiomyopathy by first amplifying sample  $\beta$ -MHC nucleic acids and performing a RNase protection assay. However, the Examiner states that Almoguera teaches methods for identifying gene mutations which include amplifying a DNA sequence by PCR and performing an RNase protection assay. In particular, the Examiner states that the assay in Almoguera identifies single-base substitutions or point mutations which are considered to be "small alterations" in the DNA.

From this, the Examiner concludes that it would have been obvious

... to have modified the method of Geisterfer-Lowrance so as to have detected the mutations associated with hypertrophic cardiomyopathy in  $\beta$ -MHC nucleic acids by amplifying the nucleic acids by PCR and detecting the presence of mutations by performing an RNase protection assay ...

It is the Examiner's further position that

... the claims are not directed to methods of diagnosis but rather only to methods for identifying mutations in the  $\beta$ -MHC gene. Geisterfer-Lowrance provides the motivation and reasonable expectation for identifying these mutations in other nucleic acid samples because the reference provides the methodology for detecting such mutations and it would have been well within the skill of the art to have practiced these conventional methods to effectively accomplish the analysis of nucleic acids for mutations. Furthermore, the reference provides the motivation to analyze additional samples for the stated mutations because the reference teaches further assays should be performed to determine if the mutation is present in other families and states that use of genetic probes to MHC mutations will be important in facilitating our understanding of the function of MHC and the cause of HC.

From this, the Examiner concludes that "the cited prior art suggests and provides a high expectation of success of employing methods for the detection of mutations in MHC."

As discussed in Applicants' remarks above, the substance of which is reiterated here, Geisterfer-Lowrance *et al.* fail to suggest the claimed invention and provide no reasonable expectation of success for formulating a method or kit for detecting the presence of mutations associated with hypertrophic cardiomyopathy. Almoguera fails to cure the deficiencies of Geisterfer-Lowrance *et al.*

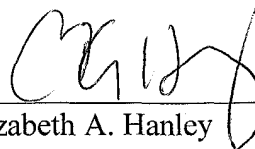
#### SUMMARY

In view of the amendments and remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining

issues or the Examiner believes that a telephone conversation with Applicant's Attorney would be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Respectfully submitted,

LAHIVE & COCKFIELD, LLP



Elizabeth A. Hanley  
Registration No. 33,505  
Attorney for Applicants

28 State Street  
Boston, MA 02109  
(617) 227-7400  
Dated: May 4, 1998